Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Trivedi MH, Walker R, Ling W, et al. Bupropion and naltrexone in methamphetamine use disorder. N Engl J Med 2021;384:140-53. DOI: 10.1056/NEJMoa2020214

Treatment of Methamphetamine Use Disorder with Bupropion and Naltrexone

Supplementary Appendix

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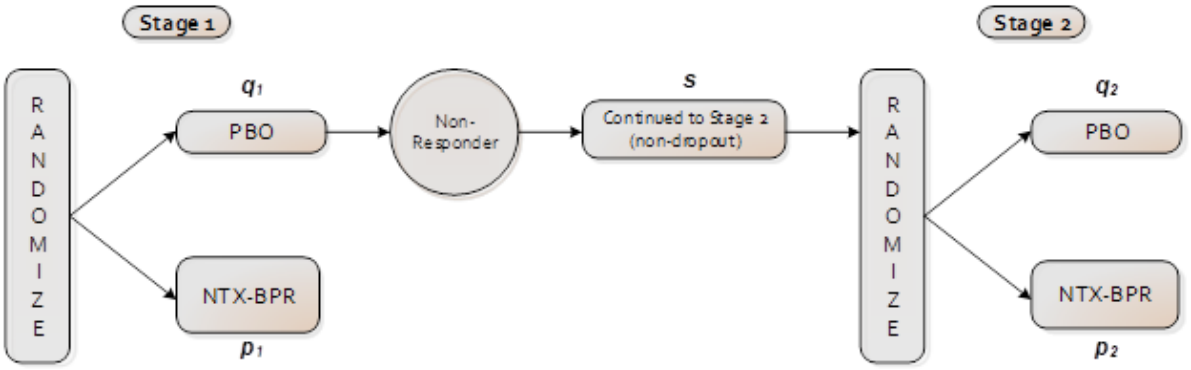
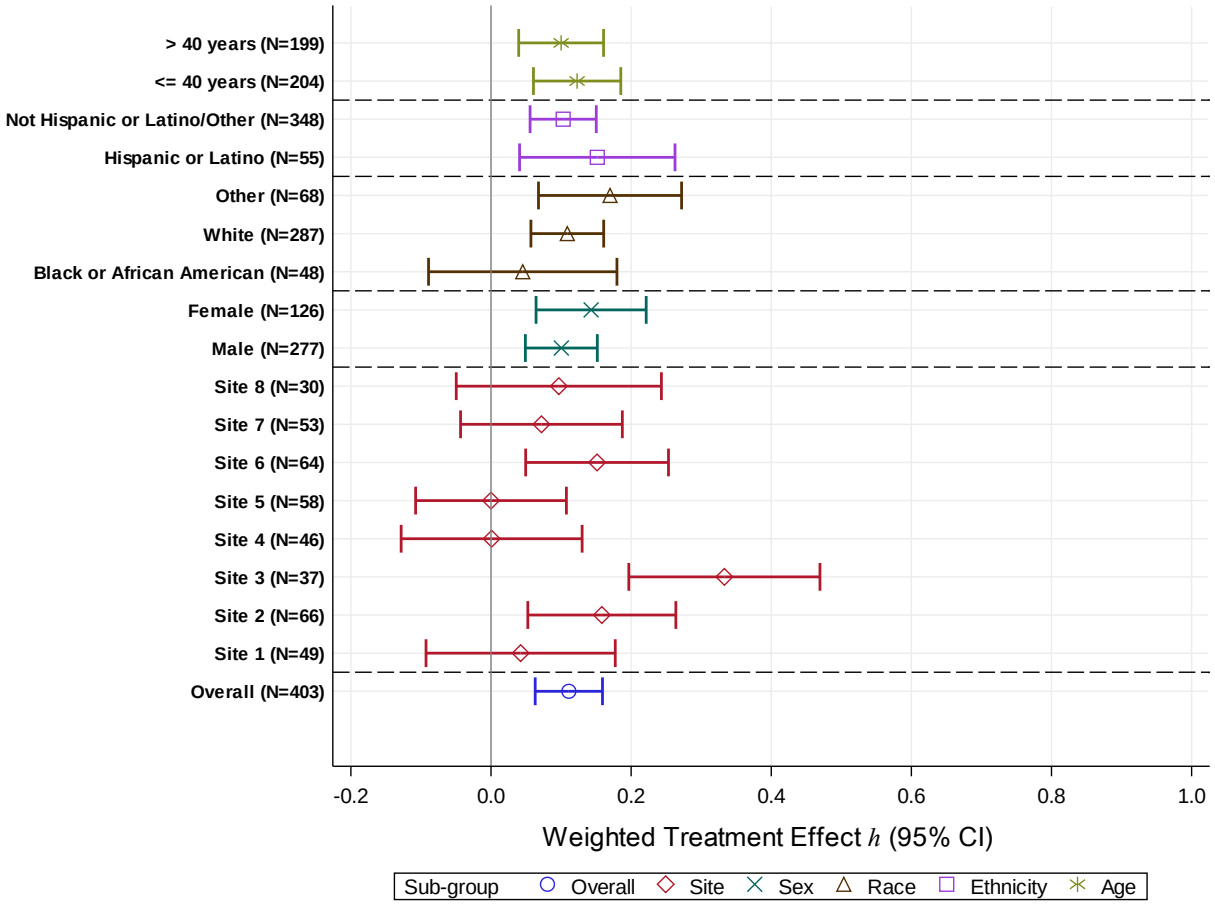
Figure S1: Schematic of the intention-to-treat population in a sequential parallel comparison design (SPCD).



A sequential parallel comparison design (SPCD) is a type of enrichment design where, by design, participants who are identified as placebo (PBO) non-responders during stage 1 are re-randomized in stage 2. Let *p1, q1* be the response rates for the naltrexone-bupropion (NTX-BPR) group and PBO group, respectively, in stage 1; let *p2, q2* be the response rates for NTX-BPR and PBO, respectively, in stage 2; let *s* be the rate of continuation into stage 2 among PBO non-responders, (i.e., *1-s* is the stage 1 drop-out rate). The intention-to-treat population in an SPCD study is defined as follows: all participants randomized to stage 1 are used to calculate the response rate in stage 1 and all participants re-randomized in stage 2 are used to calculate the response rate in stage 2. For the current study, the primary analysis alternative hypothesis is that the NTX-BPR group had a higher response rate than PBO in the full population (stage 1) OR in the sub-population of PBO non-responders (stage 2).

Figure S2: Forest plot of the overall weighted treatment effect by subgroups.



Forest plot of the overall weighted treatment effect, *h*, and 95% confidence intervals in each of the pre-specified subgroups (age, ethnicity, race, sex, and study site) and for the total sample of N=403. The vertical line at zero indicates no treatment effect. If a lower confidence limit is less than zero, the treatment effect is not significant in that subgroup. Some subgroups are small and inferences about the homogeneity of treatment effects are to be made with caution.

Table S1. Sensitivity analyses results (in the intention-to-treat population), by stage and treatment group.

	Stage 1			Stage 2			Weighted Treatment Effect Across Both Stages[1]		
		Placebo	NTX-BPR		Placebo	NTX-BPR			
Sensitivity Analyses	**N**	**Response Rate**	**Response Rate**	**N**	**Response Rate**	**Response Rate**	**Treatment Effect *h***	**Standard Error of *h***	**95% CI**
Complete cases[2]	229	9/177 (5.1%)	15/52 (28.8%)	155	1/75 (1.3%)	13/80 (16.3%)	0.187	0.036	0.116, 0.258
Weight $w = 0.50$	403	10/294 (3.4%)	18/109 (16.5%)	225	2/111 (1.8%)	13/114 (11.4%)	0.114	0.025	0.065, 0.162

NTX-BPR = injectable extended-release naltrexone plus oral bupropion group.

[1] Design parameters included the following: randomization fraction $a = 0.37$; weight $w = 0.43$ in stage 1 and $w = 0.57$ in stage 2; the observed rate of continuation into stage 2 among placebo non-responders was 0.79. The stage 1 Nis the total number of participants randomized. The stage 2 N is the number of participants re-randomized. The weighted treatment effect, *h*, was defined as the difference between the weighted average response rates in the NTX-BPR group *[w(p1) + (1-w)p2]* minus the weighted average response rate in the placebo group *[w(q1) + (1-w)q2]*. Response was defined as having at least 3 (out of 4) methamphetamine-negative UDS in the last two weeks of each stage.

[2] Complete cases are defined as participants with all four urine drug screen samples collected in the final 2 weeks of the stage.

Table S2. Treatment-emergent serious adverse events and adverse events in the safety population (all consented participants).

	Stage 1 (ITT)			Stage 2 Re-randomized (ITT)			Stage 2 Not Re-randomized		
Treatment-emergent Serious Adverse Events (SAE)	**Placebo (N=294)**	**NTX-BPR (N=109)**	***p***	**Placebo (N=111)**	**NTX-BPR (N=114)**	***p***	**Placebo (N=69)**	**NTX-BPR (N=109)**	***p***
Participants with at least one treatment emergent SAE, N (%)[1]	4 (1.4%)	1 (0.9%)	1.00	4 (3.6%)	3 (2.6%)	0.72	1 (1.4%)	3 (2.8%)	1.00
Total number of SAEs[2]	4	1		4	4		1	3	
Type of SAE, N (%)[3]									
Inpatient hospital admission or prolongation of existing hospitalization	3 (75.0%)	1 (100.0%)		4 (100.0%)	4 (100.0%)		1 (100.0%)	3 (100.0%)	
Seizure	1 (25.0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Name of SAE, N (%)									
Substance-induced psychotic disorder	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Paranoia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Homicidal ideation	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Depression	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Seizure	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Gastroenteritis	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Gastroenteritis shigella	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Pneumonia	-	-		1 (0.9%)	0 (0%)	0.49	0 (0%)	1 (0.9%)	1.00
Urosepsis	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Cellulitis	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Appendicitis	-	-		-	-		1 (1.4%)	0 (0%)	0.39
Pancreatitis	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Neck pain	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Hyperglycemia	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Cardiac failure acute	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Victim of crime	-	-		1 (0.9%)	0 (0%)	0.49	-	-	

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Participants with at least one treatment emergent AE, N (%)[1]	245 (83.3%)	99 (90.8%)	0.08	77 (69.4%)	88 (77.2%)	0.23	15 (21.7%)	59 (54.1%)	<0.001
Maximum adverse event severity for participants with at least one treatment emergent adverse event, N (%)			0.01			0.45			0.07
Grade 1 - Mild	150 (61.2%)	47 (47.5%)		47 (61.0%)	56 (63.6%)		5 (33.3%)	37 (62.7%)	
Grade 2 - Moderate	85 (34.7%)	50 (50.5%)		21 (27.3%)	26 (29.5%)		7 (46.7%)	18 (30.5%)	
Grade 3 - Severe	10 (4.1%)	1 (1.0%)		9 (11.7%)	5 (5.7%)		3 (20.0%)	4 (6.8%)	
Missing	0 (0%)	1 (1.0%)		0 (0%)	1 (1.1%)		0 (0%)	0 (0%)	
Number of treatment emergent AEs	839	417		206	295		34	148	
Severity of AE			0.09			0.02			0.85
Grade 1 - Mild	679 (80.9%)	328 (78.7%)		151 (73.3%)	246 (83.4%)		24 (70.6%)	104 (70.3%)	
Grade 2 - Moderate	149 (17.8%)	86 (20.6%)		45 (21.8%)	40 (13.6%)		7 (20.6%)	35 (23.6%)	
Grade 3 - Severe	11 (1.3%)	1 (0.2%)		10 (4.9%)	8 (2.7%)		3 (8.8%)	9 (6.1%)	
Missing	0 (0%)	2 (0.5%)		0 (0%)	1 (0.3%)		0 (0%)	0 (0%)	
Name of AE, N (%)									
Gastrointestinal disorders	**96 (32.7%)**	**66 (60.6%)**	**<0.001**	**24 (21.6%)**	**48 (42.1%)**	0.001	**4 (5.8%)**	**19 (17.4%)**	**0.04**
Nausea	45 (15.3%)	41 (37.6%)	<0.001	8 (7.2%)	32 (28.1%)	<.001	0 (0%)	6 (5.5%)	0.08
Diarrhea	18 (6.1%)	7 (6.4%)	1.00	5 (4.5%)	6 (5.3%)	1.00	1 (1.4%)	3 (2.8%)	1.00
Vomiting	6 (2.0%)	13 (11.9%)	<0.001	3 (2.7%)	12 (10.5%)	0.03	0 (0%)	3 (2.8%)	0.28
Constipation	7 (2.4%)	10 (9.2%)	0.005	3 (2.7%)	2 (1.8%)	0.68	0 (0%)	4 (3.7%)	0.16
Dry mouth	5 (1.7%)	9 (8.3%)	0.003	2 (1.8%)	1 (0.9%)	0.62	0 (0%)	1 (0.9%)	1.00
Toothache	6 (2.0%)	4 (3.7%)	0.47	4 (3.6%)	1 (0.9%)	0.21	1 (1.4%)	0 (0%)	0.39
Abdominal pain	7 (2.4%)	2 (1.8%)	1.00	0 (0%)	3 (2.6%)	0.25	0 (0%)	2 (1.8%)	0.52
Abdominal discomfort	5 (1.7%)	4 (3.7%)	0.26	2 (1.8%)	1 (0.9%)	0.62	0 (0%)	4 (3.7%)	0.16
Abdominal pain upper	1 (0.3%)	5 (4.6%)	0.006	3 (2.7%)	6 (5.3%)	0.50	1 (1.4%)	0 (0%)	0.39

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*P*
Dyspepsia	6 (2.0%)	0 (0%)	0.207	1 (0.9%)	3 (2.6%)	0.62	1 (1.4%)	1 (0.9%)	1.00
Abdominal distension	1 (0.3%)	1 (0.9%)	0.47	0 (0%)	1 (0.9%)	1.00	-	-	
Hemorrhoids	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Gastroesophageal reflux disease	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Chapped lips	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Breath odor	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Abdominal pain lower	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Vomiting projectile	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Tongue ulceration	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Stomatitis	0 (0%)	1 (0.9%)	0.27	0 (0%)	1 (0.9%)	1.00	-	-	
Salivary hypersecretion	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Rectal hemorrhage	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Pancreatitis	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Oral disorder	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Melaena	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Loose tooth	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Glossodynia	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Gastrointestinal pain	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Gastritis	0 (0%)	1 (0.9%)	0.27	0 (0%)	1 (0.9%)	1.00	-	-	
Food poisoning	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Flatulence	1 (0.3%)	0 (0%)	1.00	0 (0%)	2 (1.8%)	0.50	-	-	
Dental discomfort	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Mouth ulceration	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Gingival pain	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Eructation	-	-		-	-		0 (0%)	1 (0.9%)	1.00

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT)			Stage 2 Re-randomized (ITT)			Stage 2 Not Re-randomized		
	PBO (N=294)	**NTX-BPR (N=109)**	***p***	**PBO/PBO (N=111)**	**PBO/NTX-BPR (N=114)**	***p***	**PBO (N=69)**	**NTX-BPR (N=109)**	***p***
Nervous system disorders	**97 (33.0%)**	**38 (34.9%)**	**0.72**	**12 (10.8%)**	**28 (24.6%)**	**0.009**	**3 (4.3%)**	**10 (9.2%)**	**0.38**
Headache	68 (23.1%)	13 (11.9%)	0.01	6 (5.4%)	11 (9.6%)	0.31	3 (4.3%)	7 (6.4%)	0.74
Dizziness	8 (2.7%)	11 (10.1%)	0.006	1 (0.9%)	7 (6.1%)	0.07	0 (0%)	1 (0.9%)	1.00
Somnolence	10 (3.4%)	3 (2.8%)	1.00	1 (0.9%)	0 (0%)	0.49	0 (0%)	1 (0.9%)	1.00
Tremor	1 (0.3%)	5 (4.6%)	0.006	0 (0%)	3 (2.6%)	0.25	-	-	
Lethargy	4 (1.4%)	2 (1.8%)	0.66	0 (0%)	3 (2.6%)	0.25	-	-	
Migraine	2 (0.7%)	3 (2.8%)	0.13	0 (0%)	1 (0.9%)	1.00	-	-	
Disturbance in attention	2 (0.7%)	2 (1.8%)	0.30	-	-		-	-	
Hypoesthesia	4 (1.4%)	0 (0%)	0.58	1 (0.9%)	1 (0.9%)	1.00	-	-	
Hypersomnia	3 (1.0%)	1 (0.9%)	1.00	2 (1.8%)	0 (0%)	0.24	-	-	
Dysgeusia	2 (0.7%)	1 (0.9%)	1.00	1 (0.9%)	2 (1.8%)	1.00	-	-	
Cognitive disorder	2 (0.7%)	1 (0.9%)	1.00	-	-		-	-	
Carpal tunnel syndrome	2 (0.7%)	0 (0%)	1.00	-	-		0 (0%)	1 (0.9%)	1.00
Paresthesia	2 (0.7%)	0 (0%)	1.00	2 (1.8%)	0 (0%)	0.24	-	-	
Loss of consciousness	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Head discomfort	2 (0.7%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Depressed level of consciousness	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Cervical radiculopathy	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Syncope	0 (0%)	1 (0.9%)	0.27	0 (0%)	1 (0.9%)	1.00	-	-	
Sleep paralysis	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Sinus headache	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Seizure	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Sedation	1 (0.3%)	0 (0%)	1.00	-	-		0 (0%)	1 (0.9%)	1.00
Restless legs syndrome	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Parosmia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Balance disorder	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Nerve compression	0 (0%)	1 (0.9%)	0.27	-	-		-	-	

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Muscle contractions involuntary	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Memory impairment	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Aphasia	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Formication	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Taste disorder	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Presyncope	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Balance disorder	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Psychiatric disorders	**75 (25.5%)**	**41 (37.6%)**	**0.02**	**16 (14.4%)**	**18 (15.8%)**	**0.85**	**4 (5.8%)**	**12 (11.0%)**	**0.29**
Irritability	19 (6.5%)	6 (5.5%)	0.82	4 (3.6%)	5 (4.4%)	1.00	0 (0%)	1 (0.9%)	1.00
Anxiety	14 (4.8%)	10 (9.2%)	0.10	1 (0.9%)	1 (0.9%)	1.00	2 (2.9%)	0 (0%)	0.15
Insomnia	12 (4.1%)	6 (5.5%)	0.59	1 (0.9%)	3 (2.6%)	0.62	0 (0%)	3 (2.8%)	0.28
Libido decreased	5 (1.7%)	4 (3.7%)	0.26	0 (0%)	1 (0.9%)	1.00	-	-	
Affect lability	4 (1.4%)	4 (3.7%)	0.22	1 (0.9%)	2 (1.8%)	1.00	-	-	
Depression	6 (2.0%)	2 (1.8%)	1.00	4 (3.6%)	4 (3.5%)	1.00	1 (1.4%)	5 (4.6%)	0.41
Depressed mood	6 (2.0%)	1 (0.9%)	0.68	1 (0.9%)	1 (0.9%)	1.00	1 (1.4%)	1 (0.9%)	1.00
Abnormal dreams	4 (1.4%)	2 (1.8%)	0.66	-	-		-	-	
Initial insomnia	2 (0.7%)	3 (2.8%)	0.13	-	-		-	-	
Paranoia	4 (1.4%)	0 (0%)	0.58	1 (0.9%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00
Mood swings	4 (1.4%)	0 (0%)	0.58	-	-		-	-	
Apathy	1 (0.3%)	2 (1.8%)	0.179	-	-		0 (0%)	1 (0.9%)	1.00
Suicidal ideation	2 (0.7%)	1 (0.9%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Restlessness	3 (1.0%)	0 (0%)	0.57	-	-		-	-	
Bruxism	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Anhedonia	1 (0.3%)	1 (0.9%)	0.47	-	-		0 (0%)	1 (0.9%)	1.00
Thinking abnormal	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Stress	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Agitation	2 (0.7%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Psychotic disorder	2 (0.7%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Panic attack	1 (0.3%)	1 (0.9%)	0.47	-	-		0 (0%)	1 (0.9%)	1.00
Nightmare	2 (0.7%)	0 (0%)	1.00	-	-		0 (0%)	1 (0.9%)	1.00
Hallucination, auditory	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Hallucination	1 (0.3%)	1 (0.9%)	0.47	0 (0%)	1 (0.9%)	1.00	-	-	
Flat affect	0 (0%)	2 (1.8%)	0.07	-	-		-	-	
Anorgasmia	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Substance-induced psychotic disorder	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Somnambulism	1 (0.3%)	0 (0%)	1.00	-	-		0 (0%)	1 (0.9%)	1.00
Somatic symptom disorder	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Sleep disorder	1 (0.3%)	0 (0%)	1.00	-	-		0 (0%)	1 (0.9%)	1.00
Post-traumatic stress disorder	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Panic disorder	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Orgasm abnormal	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Nervousness	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Aggression	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Middle insomnia	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	1 (0.9%)	1.00	-	-	
Mental status changes	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Mental fatigue	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Mental disorder	0 (0%)	1 (0.9%)	1.00	-	-		-	-	
Loss of libido	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Hallucination, visual	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Euphoric mood	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Dysphoria	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Dysphemia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Disorientation	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Depressive symptom	0 (0%)	1 (0.9%)	0.27	-	-		1 (1.4%)	1 (0.9%)	1.00

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Confusional state	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Social avoidant behaviour	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Psychotic behaviour	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Mania	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Libido increased	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Homicidal ideation	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Feeling guilty	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Drug dependence	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Disorientation	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Infections and infestations	**80 (27.2%)**	**26 (23.9%)**	**0.53**	**29 (26.1%)**	**29 (25.4%)**	**1.00**	**6 (8.7%)**	**18 (16.5%)**	**0.18**
Nasopharyngitis	14 (4.8%)	6 (5.5%)	0.80	6 (5.4%)	4 (3.5%)	0.54	0 (0%)	4 (3.7%)	0.16
Upper respiratory tract infection	15 (5.1%)	2 (1.8%)	0.17	6 (5.4%)	8 (7.0%)	0.78	3 (4.3%)	2 (1.8%)	0.38
Gastroenteritis	9 (3.1%)	5 (4.6%)	0.54	1 (0.9%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00
Cellulitis	9 (3.1%)	1 (0.9%)	0.30	1 (0.9%)	4 (3.5%)	0.37	-	-	
Urinary tract infection	6 (2.0%)	3 (2.8%)	0.71	0 (0%)	3 (2.6%)	0.25	0 (0%)	2 (1.8%)	0.52
Viral infection	5 (1.7%)	1 (0.9%)	1.00	4 (3.6%)	0 (0%)	0.06	0 (0%)	2 (1.8%)	0.52
Gonorrhea	5 (1.7%)	1 (0.9%)	1.00	-	-		1 (1.4%)	-	0.39
Abscess	4 (1.4%)	1 (0.9%)	1.00	2 (1.8%)	1 (0.9%)	0.62	-	-	
Syphilis	3 (1.0%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Sinusitis	2 (0.7%)	1 (0.9%)	1.00	-	-		1 (1.4%)	2 (1.8%)	1.00
Abscess limb	2 (0.7%)	1 (0.9%)	1.00	-	-		-	-	
Vaginal infection	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Tooth abscess	2 (0.7%)	0 (0%)	1.00	-	-		0 (0%)	1 (0.9%)	1.00
Skin infection	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Sexually transmitted disease	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Pharyngitis	1 (0.3%)	1 (0.9%)	0.47	1 (0.9%)	0 (0%)	0.49	-	-	
Influenza	1 (0.3%)	1 (0.9%)	0.47	1 (0.9%)	2 (1.8%)	1.00	0 (0%)	1 (0.9%)	1.00

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Gastroenteritis viral	2 (0.7%)	0 (0%)	1.00	0 (0%)	3 (2.6%)	0.25	-	-	
Cystitis	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Conjunctivitis	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Chlamydial infection	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Conjunctivitis chlamydial	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Bronchitis	1 (0.3%)	0 (0%)	1.00	-	-		0 (0%)	2 (1.8%)	0.52
Body tinea	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Tooth infection	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Tinea pedis	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Tinea infection	-	-		1 (0.9%)	1 (0.9%)	1.00	-	-	
Anal chlamydia infection	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Respiratory tract infection	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Pyelonephritis	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Pustule	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Otitis externa	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Oropharyngeal gonococcal infection	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Oral herpes	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	2 (1.8%)	1.00	-	-	
Latent syphilis	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Infection	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Hordeolum	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Furuncle	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Ear infection	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Paronychia	-	-		0 (0%)	1 (0.9%)	1.00	1 (1.4%)	1 (0.9%)	1.00
Pyuria	-	-		1 (0.9%)	0 (0%)	0.49	0 (0%)	1 (0.9%)	1.00
Pneumonia	-	-		1 (0.9%)	0 (0%)	0.49	0 (0%)	1 (0.9%)	1.00
Breast abscess	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Urosepsis	-	-		1 (0.9%)	0 (0%)	0.49	-	-	

	Stage 1 (ITT)			Stage 2 Re-randomized (ITT)			Stage 2 Not Re-randomized		
Treatment-emergent Adverse Events (AE)	**PBO (N=294)**	**NTX-BPR (N=109)**	***p***	**PBO/PBO (N=111)**	**PBO/NTX-BPR (N=114)**	***p***	**PBO (N=69)**	**NTX-BPR (N=109)**	***p***
Urethritis	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Subcutaneous abscess	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Appendicitis	-	-		-	-		1 (1.4%)	0 (0%)	0.39
Kidney infection	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Infectious mononucleosis	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Herpes virus infection	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Gastroenteritis shigella	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Epididymitis	-	-		-	-		0 (0%)	1 (0.9%)	1.00
General disorders and administration site conditions	**64 (21.8%)**	**24 (22.0%)**	**1.00**	**15 (13.5%)**	**19 (16.7%)**	**0.58**	**1 (1.4%)**	**11 (10.1%)**	**0.03**
Fatigue	33 (11.2%)	8 (7.3%)	0.35	8 (7.2%)	7 (6.1%)	0.80	1 (1.4%)	4 (3.7%)	0.65
Pain	8 (2.7%)	1 (0.9%)	0.46	2 (1.8%)	2 (1.8%)	1.00	0 (0%)	1 (0.9%)	1.00
Pyrexia	7 (2.4%)	1 (0.9%)	0.69	1 (0.9%)	2 (1.8%)	1.00	-	-	
Asthenia	7 (2.4%)	0 (0%)	0.20	-	-		0 (0%)	3 (2.8%)	0.28
Feeling jittery	2 (0.7%)	4 (3.7%)	0.05	0 (0%)	1 (0.9%)	1.00	-	-	
Thirst	3 (1.0%)	2 (1.8%)	0.62	-	-		-	-	
Malaise	1 (0.3%)	4 (3.7%)	0.02	0 (0%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00
Chest pain	3 (1.0%)	1 (0.9%)	1.00	0 (0%)	3 (2.6%)	0.25	0 (0%)	1 (0.9%)	1.00
Peripheral swelling	4 (1.4%)	-0 (0%)	0.58	2 (1.8%)	1 (0.9%)	0.62	-	-	
Influenza like illness	1 (0.3%)	2 (1.8%)	0.18	1 (0.9%)	2 (1.8%)	1.00	-	-	
Feeling abnormal	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Feeling cold	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Energy increased	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Drug withdrawal syndrome	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Chills	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Vessel puncture site reaction	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Swelling face	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Injury associated with device	1 (0.3%)	0 (0%)	1.00	-	-		0 (0%)	1 (0.9%)	1.00

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Injection site pain	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Injection site discomfort	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Implant site pain	0 (0%)	1 (0.9%)	0.27	1 (0.9%)	0 (0%)	0.49	-	-	
Ill-defined disorder	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Tenderness	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Edema peripheral	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Injection site swelling	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Injection site hematoma	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Crying	-	-		0 (0%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00
Musculoskeletal and connective tissue disorders	**37 (12.6%)**	**18 (16.5%)**	**0.33**	**13 (11.7%)**	**9 (7.9%)**	**0.38**	**1 (1.4%)**	**8 (7.3%)**	**0.16**
Back pain	11 (3.7%)	2 (1.8%)	0.53	2 (1.8%)	2 (1.8%)	1.00	0 (0%)	1 (0.9%)	1.00
Arthralgia	6 (2.0%)	4 (3.7%)	0.47	0 (0%)	2 (1.8%)	0.50	0 (0%)	1 (0.9%)	1.00
Myalgia	6 (2.0%)	3 (2.8%)	0.71	2 (1.8%)	1 (0.9%)	0.62	0 (0%)	2 (1.8%)	0.52
Muscle spasms	6 (2.0%)	1 (0.9%)	0.68	1 (0.9%)	0 (0%)		-	-	
Pain in extremity	4 (1.4%)	3 (2.8%)	0.39	2 (1.8%)	2 (1.8%)	1.00	0 (0%)	1 (0.9%)	1.00
Musculoskeletal pain	3 (1.0%)	2 (1.8%)	0.62	1 (0.9%)	0 (0%)	0.49	1 (1.4%)	1 (0.9%)	1.00
Muscle tightness	1 (0.3%)	3 (2.8%)	0.06	-	-		-	-	
Neck pain	1 (0.3%)	3 (2.8%)	0.06	1 (0.9%)	3 (2.6%)	0.62	-	-	
Muscular weakness	2 (0.7%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Pain in jaw	2 (0.7%)	0 (0%)	1.00	2 (1.8%)	0 (0%)	0.24	-	-	
Musculoskeletal stiffness	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Flank pain	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Chest wall mass	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Bursitis	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Axillary mass	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Musculoskeletal chest pain	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00
Muscle twitching	-	-		0 (0%)	1 (0.9%)	1.00	-	-	

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Joint stiffness	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Groin pain	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Costochondritis	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Injury, poisoning and procedural complications	**35 (11.9%)**	**13 (11.9%)**	**1.00**	**16 (14.4%)**	**12 (10.5%)**	**0.42**	**2 (2.9%)**	**12 (11.0%)**	**0.08**
Skin laceration	11 (3.7%)	2 (1.8%)	0.53	2 (1.8%)	2 (1.8%)	1.00	0 (0%)	5 (4.6%)	0.16
Skin abrasion	8 (2.7%)	2 (1.8%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Contusion	5 (1.7%)	3 (2.8%)	0.45	5 (4.5%)	0 (0%)	0.03	0 (0%)	2 (1.8%)	0.52
Thermal burn	4 (1.4%)	1 (0.9%)	1.00	3 (2.7%)	0 (0%)	0.12	-	-	
Limb injury	3 (1.0%)	0 (0%)	0.57	0 (0%)	1 (0.9%)	1.00	0 (0%)	2 (1.8%)	0.52
Ligament sprain	0 (0%)	2 (1.8%)	0.07	1 (0.9%)	0 (0%)	0.49	-	-	
Wound	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Arthropod bite	0 (0%)	2 (1.8%)	0.07	1 (0.9%)	2 (1.8%)	1.00	-	-	
Tooth fracture	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Road traffic accident	1 (0.3%)	1 (0.9%)	0.47	0 (0%)	2 (1.8%)	0.50	0 (0%)	1 (0.9%)	1.00
Head injury	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Fracture	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Forearm fracture	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Fall	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Arthropod sting	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Spinal column injury	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Soft tissue injury	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Periorbital hemorrhage	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Muscle strain	0 (0%)	1 (0.9%)	0.27	0 (0%)	2 (1.8%)	0.50	0 (0%)	1 (0.9%)	1.00
Muscle rupture	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Animal bite	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Joint injury	0 (0%)	0 (0%)		2 (1.8%)	1 (0.9%)	0.62	-	-	
Eye injury	0 (0%)	0 (0%)		1 (0.9%)	1 (0.9%)	1.00	-	-	

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Facial bones fracture	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Face injury	-	-		-	-		1 (1.4%)	0 (0%)	0.39
Epicondylitis	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Concussion	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Splinter	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Procedural nausea	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Meniscus injury	-	-		-	-		0 (0%)	1 (0.9%)	
Accident at work	-	-		-	-		1 (1.4%)	0 (0%)	0.39
Intentional overdose	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Skin and subcutaneous tissue disorders	**29 (9.9%)**	**16 (14.7%)**	**0.21**	**9 (8.1%)**	**7 (6.1%)**	**0.61**	**2 (2.9%)**	**3 (2.8%)**	**1.00**
Hyperhidrosis	3 (1.0%)	8 (7.3%)	0.002	0 (0%)	2 (1.8%)	0.50	0 (0%)	1 (0.9%)	1.00
Rash	6 (2.0%)	2 (1.8%)	1.00	5 (4.5%)	2 (1.8%)	0.28	0 (0%)	2 (1.8%)	0.52
Acne	3 (1.0%)	3 (2.8%)	0.35	-	-		-	-	
Ecchymosis	3 (1.0%)	2 (1.8%)	0.62	1 (0.9%)	0 (0%)	0.49	-	-	
Night sweats	3 (1.0%)	1 (0.9%)	1.00	-	-		-	-	
Eczema	3 (1.0%)	0 (0%)	0.57	-	-		-	-	
Dry skin	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Blister	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Skin ulcer	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Hair texture abnormal	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Erythema	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Dermatitis contact	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Xeroderma	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Urticaria	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Alopecia	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Skin lesion	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	1 (1.4%)	0 (0%)	0.39

	Stage 1 (ITT)			Stage 2 Re-randomized (ITT)			Stage 2 Not Re-randomized		
Treatment-emergent Adverse Events (AE)	**PBO (N=294)**	**NTX-BPR (N=109)**	***p***	**PBO/PBO (N=111)**	**PBO/NTX-BPR (N=114)**	***p***	**PBO (N=69)**	**NTX-BPR (N=109)**	***p***
Skin exfoliation	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Seborrheic dermatitis	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Rash papular	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Pruritus	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Onychoclasis	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Madarosis	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Hand dermatitis	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Needle track marks	-	-		-	-		1 (1.4%)	0 (0%)	0.39
Livedo reticularis	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Dermatitis	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Respiratory, thoracic and mediastinal disorders	**25 (8.5%)**	**10 (9.2%)**	**0.84**	**9 (8.1%)**	**7 (6.1%)**	**0.61**	**1 (1.4%)**	**4 (3.7%)**	**0.65**
Cough	8 (2.7%)	0 (0%)	0.12	3 (2.7%)	0 (0%)	0.12	-	-	
Oropharyngeal pain	4 (1.4%)	2 (1.8%)	0.66	3 (2.7%)	3 (2.6%)	1.00	0 (0%)	1 (0.9%)	1.00
Nasal congestion	5 (1.7%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Sinus congestion	6 (2.0%)	0 (0%)	0.20	5 (4.5%)	2 (1.8%)	0.23	1 (1.4%)	0 (0%)	0.39
Rhinorrhea	1 (0.3%)	3 (2.8%)	0.06	1 (0.9%)	0 (0%)	0.49	0 (0%)	1 (0.9%)	1.00
Dyspnea	1 (0.3%)	3 (2.8%)	0.06	1 (0.9%)	1 (0.9%)	1.00	-	-	
Upper-airway cough syndrome	3 (1.0%)	0 (0%)	0.57	-	-		0 (0%)	1 (0.9%)	1.00
Rhinitis allergic	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Productive cough	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Epistaxis	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Dysphonia	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Yawning	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Oropharyngeal plaque	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Metabolism and nutrition disorders	**19 (6.5%)**	**12 (11.0%)**	**0.14**	**4 (3.6%)**	**8 (7.0%)**	**0.38**	**0 (0%)**	**3 (2.8%)**	**0.28**
Decreased appetite	6 (2.0%)	8 (7.3%)	0.03	3 (2.7%)	3 (2.6%)	1.00	0 (0%)	1 (0.9%)	1.00
Increased appetite	8 (2.7%)	2 (1.8%)	1.00	1 (0.9%)	0 (0%)	0.49	0 (0%)	1 (0.9%)	1.00

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Dehydration	1 (0.3%)	2 (1.8%)	0.18	-	-		0 (0%)	1 (0.9%)	1.00
Polydipsia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Hyperproteinemia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Hyponatremia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Hypocalcaemia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Hypoalbuminemia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Alcohol intolerance	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Hypoglycemia	-	-		0 (0%)	2 (1.8%)	0.50	-	-	
Vitamin D deficiency	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Hyperglycemia	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Gout	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Investigations	**16 (5.4%)**	**8 (7.3%)**	**0.48**	**4 (3.6%)**	**9 (7.9%)**	**0.25**	**1 (1.4%)**	**4 (3.7%)**	**0.65**
Blood pressure increased	6 (2.0%)	3 (2.8%)	0.71	0 (0%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00
Weight increased	6 (2.0%)	1 (0.9%)	0.68	0 (0%)	1 (0.9%)	1.00	-	-	
Blood creatinine increased	0 (0%)	2 (1.8%)	0.07	0 (0%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00
Blood bilirubin increased	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Red blood cell count decreased	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Liver function test increased	0 (0%)	1 (0.9%)	0.27	-	-		1 (1.4%)	0 (0%)	0.39
Hepatic enzyme increased	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00
Blood pressure diastolic increased	1 (0.3%)	0 (0%)	1.00	-	-		0 (0%)	1 (0.9%)	1.00
Blood glucose increased	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Blood glucose decreased	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
White blood cell count increased	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Weight decreased	0 (0%)	1 (0.9%)	0.27	1 (0.9%)	2 (1.8%)	1.00	-	-	
Neutrophil count decreased	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Electrocardiogram change	-	-		0 (0%)	1 (0.9%)	1.00	-	-	

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Blood urine present	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Blood pressure decreased	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Renal function test abnormal	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Platelet count increased	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Reproductive system and breast disorders	**13 (4.4%)**	**5 (4.6%)**	**1.00**	**5 (4.5%)**	**3 (2.6%)**	**0.50**	**1 (1.4%)**	**2 (1.8%)**	**1.00**
Erectile dysfunction	4 (1.4%)	2 (1.8%)	0.66	0 (0%)	1 (0.9%)	1.00	-	-	
Dysmenorrhea	2 (0.7%)	1 (0.9%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Penis disorder	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Penile discharge	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Menstrual disorder	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Erection increased	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Ejaculation delayed	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Cervical dysplasia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Vulvovaginal pruritus	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Vaginal discharge	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Testicular pain	1 (0.3%)	0 (0%)	1.00	-	-		1 (1.4%)	0 (0%)	0.39
Balanoposthitis	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Sexual dysfunction	1 (0.3%)	0 (0%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Metrorrhagia	-	-		1 (0.9%)	0 (0%)	0.49	0 (0%)	1 (0.9%)	1.00
Vaginal odor	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Pelvic pain	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Genital lesion	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Benign prostatic hyperplasia	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Renal and urinary disorders	**9 (3.1%)**	**2 (1.8%)**	**0.73**	**3 (2.7%)**	**2 (1.8%)**	**0.68**	**1 (1.4%)**	**1 (0.9%)**	**1.00**
Pollakiuria	3 (1.0%)	0 (0%)	0.57	-	-		-	-	
Micturition urgency	2 (0.7%)	1 (0.9%)	1.00	-	-		-	-	
Dysuria	1 (0.3%)	1 (0.9%)	0.47	1 (0.9%)	1 (0.9%)	1.00	1 (1.4%)	0 (0%)	0.39

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Urine abnormality	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Urinary hesitation	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Proteinuria	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Micturition frequency decreased	0 (0%)	1 (0.9%)	1.00	-	-		-	-	
Nocturia	-	-		1 (0.9%)	1 (0.9%)	1.00	-	-	
Hematuria	-	-		1 (0.9%)	0 (0%)	0.49	1 (1.4%)	0 (0%)	0.39
Polyuria	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Vascular disorders	**5 (1.7%)**	**5 (4.6%)**	0.14	**1 (0.9%)**	**3 (2.6%)**	**0.62**	**0 (0%)**	**2 (1.8%)**	**0.52**
Flushing	1 (0.3%)	3 (2.8%)	0.06	-	-		-	-	
Hypertension	2 (0.7%)	1 (0.9%)	1.00	-	-		-	-	
Hot flush	1 (0.3%)	2 (1.8%)	0.18	-	-		0 (0%)	1 (0.9%)	1.00
Orthostatic hypotension	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Hematoma	-	-		0 (0%)	2 (1.8%)	0.50	-	-	
Thrombophlebitis superficial	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Thrombophlebitis	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Hypotension	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Eye disorders	**8 (2.7%)**	**1 (0.9%)**	0.46	**1 (0.9%)**	**2 (1.8%)**	**1.00**	**0 (0%)**	**1 (0.9%)**	**1.00**
Vitreous floaters	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Visual impairment	1 (0.3%)	1 (0.9%)	0.47	-	-		-	-	
Eye pruritus	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Diplopia	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Pupils unequal	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Photophobia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Eye discharge	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Dry eye	1 (0.3%)	0 (0%)	1.00	-	-		0 (0%)	1 (0.9%)	1.00
Ocular hyperemia	-	-		1 (0.9%)	1 (0.9%)	1.00	-	-	
Eye irritation	-	-		0 (0%)	1 (0.9%)	1.00	-	-	

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Blood and lymphatic system disorders	**5 (1.7%)**	**1 (0.9%)**	1.00	**0 (0%)**	**1 (0.9%)**	**1.00**	**0 (0%)**	**0 (0%)**	-
Lymphadenopathy	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Leukocytosis	1 (0.3%)	1 (0.9%)	0.47	0 (0%)	1 (0.9%)	1.00	-	-	
Anemia	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Eosinophilia	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Ear and labyrinth disorders	**4 (1.4%)**	**1 (0.9%)**	1.00	**1 (0.9%)**	**3 (2.6%)**	**0.62**	**1 (1.4%)**	**0 (0%)**	**0.39**
Tinnitus	2 (0.7%)	1 (0.9%)	1.00	0 (0%)	2 (1.8%)	0.50	-	-	
Motion sickness	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Ear pain	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Vertigo	-	-		0 (0%)	1 (0.9%)	1.00	-	-	
Cerumen impaction	-	-		-	-		1 (1.4%)	0 (0%)	0.39
Immune system disorders	**3 (1.0%)**	**0 (0%)**	0.57	**1 (0.9%)**	**0 (0%)**	**0.49**	**0 (0%)**	**0 (0%)**	-
Seasonal allergy	2 (0.7%)	0 (0%)	1.00	-	-		-	-	
Hypersensitivity	1 (0.3%)	0 (0%)	1.00	1 (0.9%)	0 (0%)	0.49	-	-	
Cardiac disorders	**2 (0.7%)**	**1 (0.9%)**	1.00	**0 (0%)**	**1 (0.9%)**	**1.00**	**0 (0%)**	**1 (0.9%)**	**1.00**
Palpitations	2 (0.7%)	1 (0.9%)	1.00	0 (0%)	1 (0.9%)	1.00	-	-	
Cardiac failure acute	-	-		-	-		0 (0%)	1 (0.9%)	1.00
Social circumstances	**1 (0.3%)**	**2 (1.8%)**	0.18	**1 (0.9%)**	**0 (0%)**	**0.49**	**1 (1.4%)**	**0 (0%)**	**0.39**
Physical assault	1 (0.3%)	2 (1.8%)	0.18	-	-		1 (1.4%)	0 (0%)	0.39
Victim of crime	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Hepatobiliary disorders	**1 (0.3%)**	**0 (0%)**	1.00	**0 (0%)**	**0 (0%)**	-	**0 (0%)**	**0 (0%)**	-
Hyperbilirubinemia	1 (0.3%)	0 (0%)	1.00	-	-		-	-	
Neoplasms benign, malignant and unspecified (includes cysts and polyps)	**0 (0%)**	**1 (0.9%)**	0.27	**0 (0%)**	**0 (0%)**	-	**0 (0%)**	**0 (0%)**	-
Benign neoplasm of skin	0 (0%)	1 (0.9%)	0.27	-	-		-	-	
Surgical and medical procedures	**0 (0%)**	**0 (0%)**	**-**	**1 (0.9%)**	**0 (0%)**	**0.49**	**1 (1.4%)**	**1 (0.9%)**	**1.00**
Hospitalization	-	-		-	-		1 (1.4%)	0 (0%)	0.39
Endodontic procedure	-	-		-	-		0 (0%)	1 (0.9%)	1.00

Treatment-emergent Adverse Events (AE)	Stage 1 (ITT) PBO (N=294)	Stage 1 (ITT) NTX-BPR (N=109)	*p*	Stage 2 Re-randomized (ITT) PBO/PBO (N=111)	Stage 2 Re-randomized (ITT) PBO/NTX-BPR (N=114)	*p*	Stage 2 Not Re-randomized PBO (N=69)	Stage 2 Not Re-randomized NTX-BPR (N=109)	*p*
Anal lesion excision	-	-		1 (0.9%)	0 (0%)	0.49	-	-	
Endocrine disorders	**0 (0%)**	**0 (0%)**	**-**	**0 (0%)**	**0 (0%)**	**-**	**1 (1.4%)**	0 (0%)	**0.39**
Goiter	-	-		-			1 (1.4%)	0 (0%)	0.39

NTX-BPR = injectable extended-release naltrexone plus oral bupropion group.

[1] Stage 1 SAEs and AEs include events occurring for all randomized participants before the start of stage 2. Stage 2 SAEs and AEs include events occurring on or after the date of re-randomization for re-randomized participants and in Weeks 7 or later for non-re-randomized participants.

[2] SAEs presented here include all treatment-emergent SAEs for the safety population. Four SAEs occurred after screening but prior to randomization, and are not presented. These non-treatment emergent SAEs were Hypertensive crisis, Genitourinary chlamydia infection, Neurosyphilis, and Appendicitis.

[3] SAEs were classified into 7 categories: Death, Life-threatening event, Persistent or significant incapacity, Seizure, Inpatient hospital admission or prolongation of existing hospitalization, Congenital anomaly or birth defect, or Medical event that required intervention to prevent any of the above.